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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	John G. Bauman et al.
Application No.	:	10/782,024
Filed	:	February 18, 2004
For	:	LIPOXIN A_4 ANALOGS
Examiner	:	Deborah D. Carr
Art Unit	:	1621
Docket No.	:	140140.401C1
Date	:	March 16, 2005

Mail Stop Amendment
Director of the United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Director of the United States Patent and Trademark Office:

PETITION TO WITHDRAW FINALITY OF RESTRICTION REQUIREMENT

This petition to withdraw finality of the restriction requirement is filed in response to an Office Action in the above-referenced application mailed December 16, 2004. This petition is submitted in duplicate and the fee necessary for this petition is enclosed. The Director is hereby authorized to charge any fees associated with this communication or credit any overpayment to Deposit Account No. 19-1090.

REMARKS

Applicants respectfully petition the Commissioner to withdraw the finality of the restriction requirement imposed by the Examiner in the Office Action mailed December 16, 2004. As discussed in more detail below, Applicants retain their right to submit this petition by having traversed the restriction requirement when it was first imposed in an Office Action mailed August 25, 2005. The facts underlying this request are as follows:

In an Office Action mailed August 25, 2005, the Examiner imposed a restriction to one of the following inventions is required under 35 U.S.C. §121:

Group I: Claims 1-5, drawn to Lipoxin A_4 analogs, classified in various classes and subclasses.

Group II: Claims 6-7, 10-12, 15-17, drawn to method of treating inflammatory or autoimmune disorders and pharmaceutical compositions thereof, classified in class **514**, various subclasses.

Group III: Claims 8-9, 13-14, drawn to method of treating pulmonary or respiratory tract inflammation and compositions thereof, classified in class **514**, various subclasses.

In particular, the Examiner contended that:

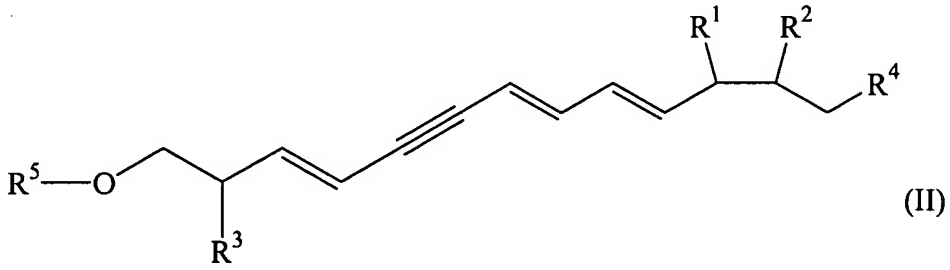
> Inventions I and II are related as product and process of use. The inventions can be shown to be distinct in either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the product can be used in a materially different process of using such as the method claimed in Group III.
>
> Inventions I and III are related as product and process of use. The inventions can be shown to be distinct in either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the product can be used in a materially different process of using such as the method claimed in Group II.

The Examiner further stated that because the inventions were distinct for the reasons given, because the inventions had acquired a separate status in the art as shown by their different classifications and because the search required for Group I was not required for Groups II or III, restriction for examination purposes is proper.

The Examiner also required the election of a single species for examination.

In the Response filed September 27, 2004, Applicants elected, **with traverse,** Group I, *i.e.*, Claims 1-5 and set forth the following arguments.

Applicants first pointed out that Claims 1-17 of the instant application are directed to compounds of the following formula (II), pharmaceutical compositions containing such compounds, and methods of using such compounds:



(II)

(where R^1, R^2, R^3, R^4 and R^5 are as described in Claim 1 of Appendix A, which is attached hereto.)

Applicants then argued that the Examiner had not established that examination of all of these claims in a single application would create a serious burden on the PTO. Applicants noted, pursuant to § 808.02 of the *Manual of Patent Examining Procedures*, the Examiner must show by appropriate explanation one of the following:

(a) **Separate classification thereof.**

(b) **A separate status in the art when [the inventions] are classified together.**

(c) **A different field of search.**

Applicants argued that the Examiner had not provided any evidence that the invention of Group I would be classified in a separate classification than the invention of Group II and/or the invention of Group III. Applicants noted that, instead, the Examiner specifically stated in the Restriction Requirement that Group II and Group III were classified in the **same** class.

Applicants further argued that even if the inventions were classified together, the Examiner has not provided any clear indication that a separate status in the art exists between the inventions or that the inventions would require different fields of search.

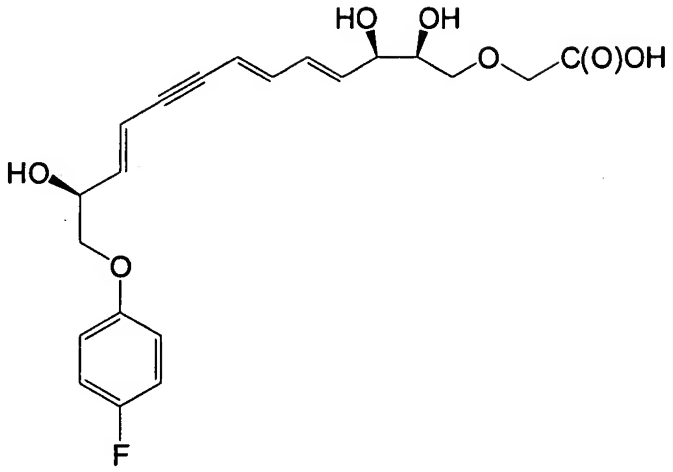
Applicants noted that the unifying feature of all the claims in the application is the compounds of formula (II). Applicants respectfully submitted that a search directed to these compounds would necessarily identify art related to methods of using such compounds and pharmaceutical compositions containing such compounds.

Applicants submitted that, in view of the Examiner's lack of evidence as to the separate classification, separate status in the art and/or different fields of search for the inventions and in view of the fact that a search directed to the compounds Group I would necessarily identify art relevant to the methods and pharmaceutical compositions of Group II and Group III, the Examiner could not support a contention of serious burden on the PTO to examine all the claims in one application.

Accordingly, Applicants respectfully requested the withdrawal of the Restriction Requirement and respectfully requested the examination of all the claims in the instant application.

In the event that the Examiner refused to withdraw the Restriction Requirement and made it final, Applicants respectfully requested that the claims in Group II or the claims in Group III be rejoined with the claims of Group I for examination as set forth in § 806.05(i) of the *Manual of Patent Examining Procedures*. In the event that the Restriction Requirement was made final, Applicants reserved the right under 35 U.S.C. 121 to file divisional applications on any non-elected subject matter.

In addition to making the foregoing arguments, Applicants elected the species of the following formula for examination:



This compound is a compound of formula (II) as set forth in Claim 1. It is prepared as described in the specification as originally filed in Example 3 and specifically claimed in Claim 5 as (5*S*,6*R*,7*E*,9*E*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-3-oxahexadeca-7,9,13-trien-11-ynoic acid. Claims 1-17 read on this species.

In the Office Action mailed December 16, 2004, the Examiner acknowledged Applicants' election with traverse of Group I (Claims 1-5) in the response filed on September 27, 2004. However, the Examiner found the grounds for the traversal to not be persuasive. The Examiner contended that the compounds contained in formula (II) covered the following classes: Classes 548 and 549 when R^1 and R^2 together form a heterocyclic ring, and Classes 554, 558, 560 and 568 for the various R^4 groups. The Examiner contended that "[t]rying to figure out the possible combination of compounds based on the various R groups would be a burden on the office". The Examiner then stated that the "requirement is still deemed proper and is therefore made final".

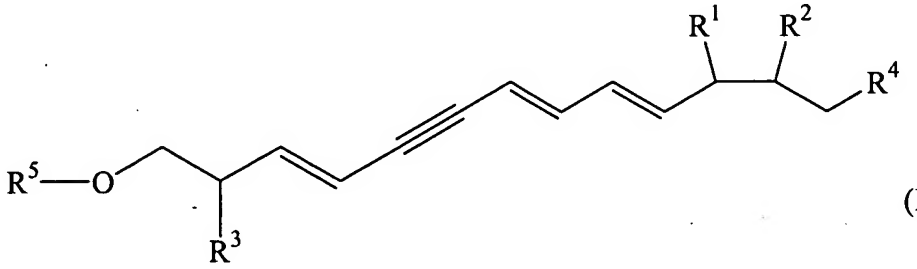
The Examiner further went on to contend that the "claims will be rejoined and examined in view of the election of species." The Examiner acknowledged that the Applicants had elected a species wherein R^4 is $-R^9-O-R^{10}-R^{11}$, R^5 is halo-substituted aryl and R^{1-3} is -OH. The Examiner further noted that this "species for search purposes will be expanded to read on this compound broadly without substitutions." The Examiner finally noted that if this species is not found

(presumably in the search), the search will be expanded to the next species wherein R^4 will be changed starting with the first moiety (presumably for R^4) listed.

It is noted that the Examiner further stated in the part of the Office Action directed to prior art rejections that Claims 3-5 were **withdrawn from consideration as being directed to non-elected subject matter.**

For the following reasons, Applicants respectfully submit that this statement is inconsistent with the Examiner's previous acknowledgement of Applicants' election of species and therefore respectfully request that the finality of the restriction requirement be withdrawn, especially with respect to the Examiner's withdrawal of Claims 3-5 from consideration as being directed to non-elected subject matter.

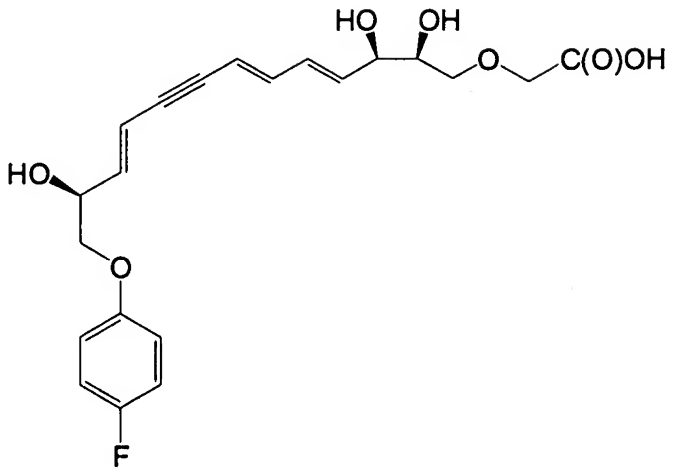
As noted above, Claims 1-17 of the instant application are directed to compounds of the following formula (II), pharmaceutical compositions containing such compounds, and methods of using such compounds:



(II)

wherein R^1, R^2, R^3, R^4 and R^5 are as defined in Claim 1 in the attached Appendix A.:

Also, as noted above, Applicants elected the following species for examination.



This compound reads on Claims 1, 2, **3, 4 and 5**. Specifically, this compound is a compound of formula (II) where:

R^1, R^2 and R^3 are each $-OR^6$ (where each R^6 is hydrogen);

R^4 is $-R^9-O-R^{10}-R^{11}$ (where R^9 is a direct bond, R^{10} is methylene and R^{11} is $-C(O)OR^7$ (where R^7 is hydrogen)); and

R^5 is aryl substituted by halo (specifically, 4-fluorophenyl).

These choices for R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^9, R^{10} and R^{11} are <u>all</u> covered by the choices for the same groups in Claims 3, 4 and 5 (see attached Appendix A). In fact, Claim 5 specifically discloses the elected species and Claims 3 and 4 <u>only</u> cover those compounds wherein R^4 is $-R^9-O-R^{10}-R^{11}$. Although Claims 3, 4 and 5 do cover other species of the invention than the elected species, they also cover elected subject matter. Thus, Claims 3, 4 and 5 should not be withdrawn from consideration but should be examined as the Examiner originally proposed.

In addition to the above inconsistencies with respect to the elected species and the withdrawn claims, Applicants respectfully submit that the Examiner did not fully considered Applicant's arguments with respect to traversing the restriction requirement. Applicants did not argue that the restriction requirement was improper **between the groups of compounds covered by Group I**, but instead Applicants argued that the restriction requirement was improper **between Group I and Group II** or **between Group I and Group III**. The reasons given by the Examiner in the instant Office Action would lead one to think that the restriction requirement

was **between the various groups of compounds encompassed by formula (II)**. Such was not the case. In fact, the Examiner grouped **all** of the compounds of formula (II) into **one** group, *i.e.*, Group I. To state that the original restriction requirement is proper because the compounds **in Group I** can be classified in different classifications does not address Applicants' arguments with respect to whether or not Group I is in a separate classification than Group II or whether or not Group I is in a separate classification than Group III, as required under § 808.02 of the *Manual of Patent Examining Procedures*.

Accordingly, for the foregoing reasons, Applicants request herein that the finality of the restriction requirement be withdrawn and that the Examiner reconsider Applicants' previous arguments with respect to the restriction requirement. In addition, Applicants specifically request that Claims 3, 4 and 5 be considered by the Examiner in view of the fact that these claims specifically cover the elected species.

This Petition is submitted herewith in duplicate with the appropriate fee.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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Appendix A (pending Claims)

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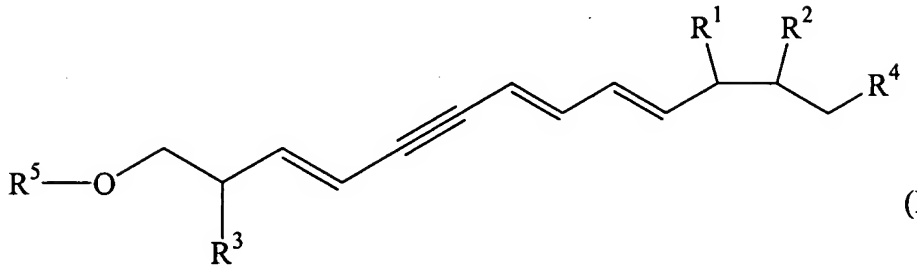
Appendix A
Pending Claims
Application No. 10/782,024

1. A compound of formula (II):

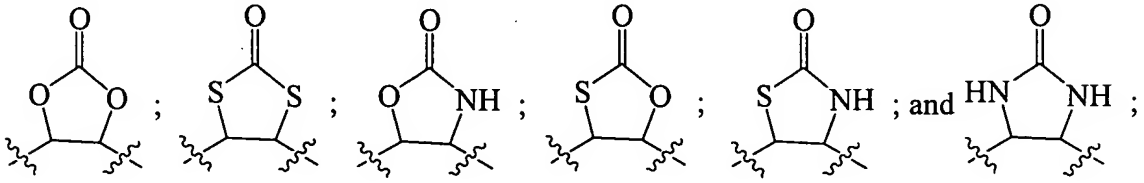


(II)

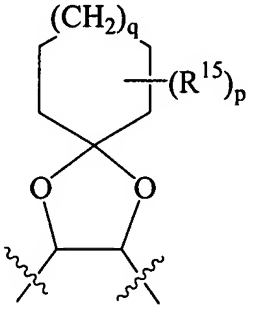
wherein:

each R^1, R^2 and R^3 are independently halo, $-OR^6$, $-SR^6$, $-S(O)_tR^7$ (where t is 1 or 2) or $-N(R^7)R^8$;

or R^1 and R^2 together with the carbons to which they are attached form a monocyclic heterocyclic structure selected from the following:



or R^1 and R^2 together with the carbons to which they are attached form the following bicyclic heterocyclic structure:



(where q is 0 to 3, p is 1 to 4 and each R^{15} is hydrogen, alkyl, aralkyl or aryl);

each R^4 is $-R^9-R^{12}$, $-R^9-R^{13}-R^{11}$, $-R^9-O-R^{10}-R^{11}$, $-R^9-O-R^{12}$, $-R^9-C(O)-R^{10}-R^{11}$, $-R^9-N(R^7)-R^{10}-R^{11}$, $-R^9-S(O)_t-R^{10}-R^{11}$ (where t is 0 to 2), or $-R^9-C(F)_2-R^9-R^{11}$;

each R^5 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy) or aralkyl (optionally

substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy);

each R^6 is independently hydrogen, alkyl, aryl, aralkyl, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^{14}$, $-C(S)OR^{14}$, $-C(O)N(R^7)R^8$, or $-C(S)N(R^7)R^8$;

each R^7 is independently hydrogen, alkyl, cycloalkyl, aryl, or aralkyl;

R^8 is independently hydrogen, alkyl, aryl, aralkyl, $-C(O)R^7$, $-C(O)OR^{14}$, or cycloalkyl (optionally substituted with one more substituents selected from the group consisting of alkyl, $-N(R^7)_2$, and $-C(O)OR^7$);

each R^9 is independently a direct bond or a straight or branched alkylene chain;

each R^{10} is independently a straight or branched alkylene chain, a straight or branched alkenylene chain, a straight or branched alkynylene chain or a cycloalkylene;

each R^{11} is independently $-C(O)OR^7$, $-C(O)N(R^7)_2$, $-P(O)(OR^7)_2$, $-S(O)_2OR^7$, $-S(O)_2N(H)R^7$ or tetrazole;

R^{12} is aryl (substituted by $-C(O)OR^7$ or $-C(O)N(R^7)_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy) or aralkyl (substituted by $-C(O)OR^7$ or $-C(O)N(R^7)_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy);

R^{13} is a branched alkylene chain, a straight or branched alkenylene chain or a cycloalkylene; and

R^{14} is alkyl, aryl or aralkyl;

as a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers; or as a cyclodextrin clathrate thereof, or as a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein:

R^1, R^2 and R^3 are each independently halo, $-OR^6$, $-SR^6$ or $-N(R^7)R^8$;

each R^4 is $-R^9-R^{12}$, $-R^9-R^{13}-R^{11}$, $-R^9-O-R^{10}-R^{11}$, $-R^9-O-R^{12}$, $-R^9-C(O)-R^{10}-R^{11}$, $-R^9-N(R^7)-R^{10}-R^{11}$, $-R^9-S(O)_t-R^{10}-R^{11}$ (where t is 0 to 2), or $-R^9-C(F)_2-R^9-R^{11}$;

R^5 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, and haloalkoxy) or aralkyl (optionally substituted by one or more

substituents selected from the group consisting of alkyl, alkoxy, halo, and haloalkoxy);

each R^6 is independently hydrogen, alkyl, aralkyl, -C(O)R^7 or -C(O)OR^7;

each R^7 is independently hydrogen, alkyl, aryl, or aralkyl;

R^8 is independently hydrogen, alkyl, aryl, aralkyl, or cycloalkyl (optionally substituted with one more substituents selected from the group consisting of alkyl, -N(R^7)$_2$, and -C(O)OR^7);

each R^9 is independently a direct bond or a straight or branched alkylene chain;

each R^{10} is independently a straight or branched alkylene chain, a straight or branched alkenylene chain, a straight or branched alkynylene chain or a cycloalkylene;

each R^{11} is independently –C(O)OR^7 or –C(O)N(R^7)$_2$;

R^{12} is aryl (substituted by –C(O)OR^7 or –C(O)N(R^7)$_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo and haloalkoxy) or aralkyl (substituted by –C(O)OR^7 or –C(O)N(R^7)$_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo and haloalkoxy);

R^{13} is a branched alkylene chain, a straight or branched alkenylene chain or a cycloalkylene.

3. The compound of Claim 2 wherein:

R^1, R^2 and R^3 are each independently halo, -OR^6, or -SR^6;

R^4 is -R^9-O-R^{10}-R^{11};

R^5 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, and haloalkoxy) or aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, and haloalkoxy);

each R^6 is independently hydrogen, alkyl, aryl, or aralkyl;

each R^7 is independently hydrogen, alkyl, aryl, or aralkyl;

R^9 is a direct bond or a straight or branched alkylene chain;

R^{10} is an straight or branched alkylene chain, a straight or branched alkenylene chain, a straight or branched alkynylene chain or a cycloalkylene; and

R^{11} is –C(O)OR^7 or –C(O)N(R^7)$_2$.

4. The compound of Claim 3 wherein:

R^1, R^2 and R^3 are each $-OR^6$;

R^4 is $-R^9-O-R^{10}-R^{11}$;

R^5 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, and haloalkoxy);

R^6 is hydrogen, alkyl, aryl, or aralkyl;

each R^7 is independently hydrogen, alkyl, aryl, or aralkyl;

R^9 is a direct bond;

R^{10} is a straight or branched alkylene chain, a straight or branched alkenylene chain, or a straight or branched alkynylene chain; and

R^{11} is $-C(O)OR^7$ or $-C(O)N(R^7)_2$.

5. The compound of Claim 4 selected from the group consisting of the following:

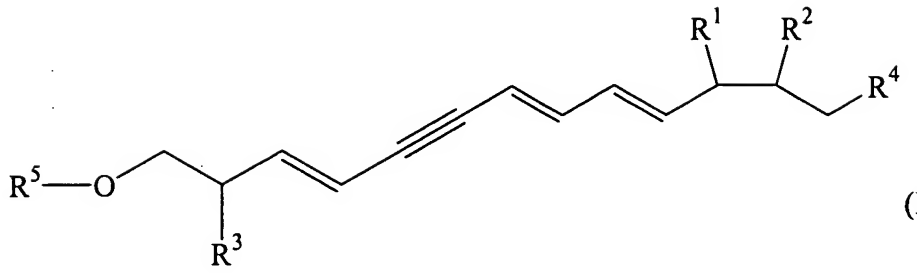
(5*S*,6*R*,7*E*,9*E*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-3-oxahexadeca-7,9,13-trien-11-ynoic acid, methyl ester;

(5*S*,6*R*,7*E*,9*E*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-3-oxahexadeca-7,9,13-trien-11-ynoic acid;

(5*S*,6*S*,7*E*,9*E*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-3-oxahexadeca-7,9,13-trien-11-ynoic acid, methyl ester; and

(5*S*,6*S*,7*E*,9*E*,13*E*,15*S*)-16-(4-fluorophenoxy)-5,6,15-trihydroxy-3-oxahexadeca-7,9,13-trien-11-ynoic acid.

6. A pharmaceutical composition useful in treating an inflammatory or autoimmune disorder in a mammal, which composition comprises one or more pharmaceutically acceptable excipient(s) and a therapeutically effective amount of a compound of formula (II):

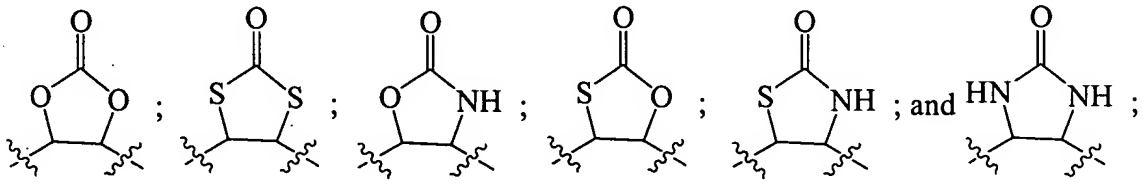


(II)

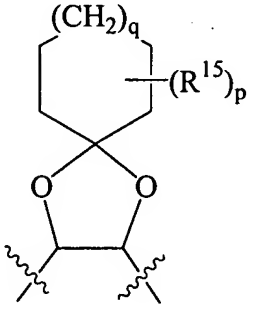
wherein:

each R^1, R^2 and R^3 are independently halo, $-OR^6$, $-SR^6$, $-S(O)_tR^7$ (where t is 1 or 2) or $-N(R^7)R^8$;

or R^1 and R^2 together with the carbons to which they are attached form a monocyclic heterocyclic structure selected from the following:



or R^1 and R^2 together with the carbons to which they are attached form the following bicyclic heterocyclic structure:



(where q is 0 to 3, p is 1 to 4 and each R^{15} is hydrogen, alkyl, aralkyl or aryl);

each R^4 is $-R^9-R^{12}$, $-R^9-R^{13}-R^{11}$, $-R^9-O-R^{10}-R^{11}$, $-R^9-O-R^{12}$, $-R^9-C(O)-R^{10}-R^{11}$, $-R^9-N(R^7)-R^{10}-R^{11}$, $-R^9-S(O)_t-R^{10}-R^{11}$ (where t is 0 to 2), or $-R^9-C(F)_2-R^9-R^{11}$;

each R^5 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy) or aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy);

each R^6 is independently hydrogen, alkyl, aryl, aralkyl, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^{14}$,

$-C(S)OR^{14}$, $-C(O)N(R^7)R^8$, or $-C(S)N(R^7)R^8$;

each R^7 is independently hydrogen, alkyl, cycloalkyl, aryl, or aralkyl;

R^8 is independently hydrogen, alkyl, aryl, aralkyl, $-C(O)R^7$, $-C(O)OR^{14}$, or cycloalkyl (optionally substituted with one more substituents selected from the group consisting of alkyl, $-N(R^7)_2$, and $-C(O)OR^7$);

each R^9 is independently a direct bond or a straight or branched alkylene chain;

each R^{10} is independently a straight or branched alkylene chain, a straight or branched alkenylene chain, a straight or branched alkynylene chain or a cycloalkylene;

each R^{11} is independently $-C(O)OR^7$, $-C(O)N(R^7)_2$, $-P(O)(OR^7)_2$, $-S(O)_2OR^7$, $-S(O)_2N(H)R^7$ or tetrazole;

R^{12} is aryl (substituted by $-C(O)OR^7$ or $-C(O)N(R^7)_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy) or aralkyl (substituted by $-C(O)OR^7$ or $-C(O)N(R^7)_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy);

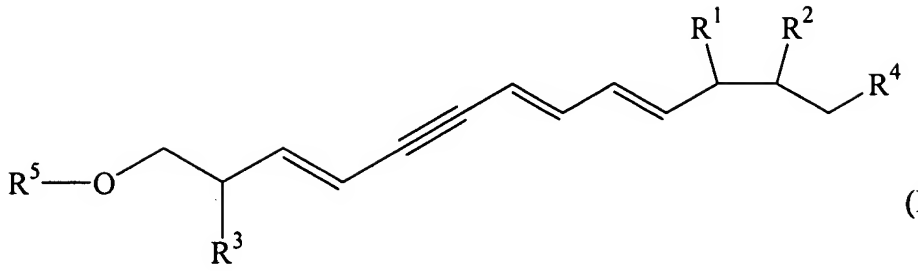
R^{13} is a branched alkylene chain, a straight or branched alkenylene chain or a cycloalkylene; and

R^{14} is alkyl, aryl or aralkyl;

as a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers; or as a cyclodextrin clathrate thereof, or as a pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition of Claim 6 wherein the mammal is a human.

8. A pharmaceutical composition useful in treating pulmonary or respiratory tract inflammation in a mammal, wherein the composition comprises one or more pharmaceutically acceptable excipient(s) and a therapeutically effective amount of a compound of formula (II):

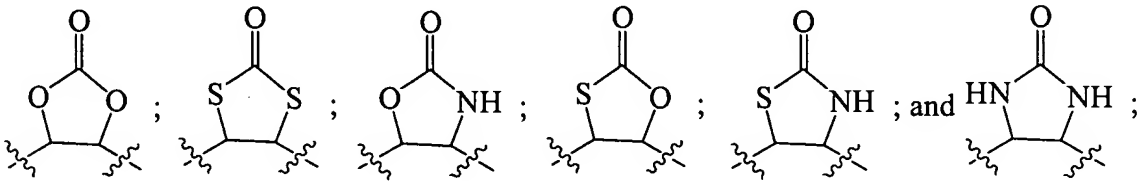


(II)

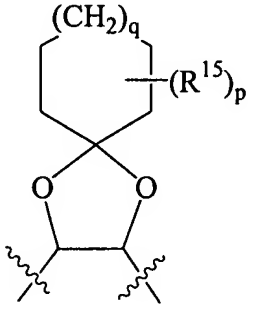
wherein:

each R^1, R^2 and R^3 are independently halo, $-OR^6$, $-SR^6$, $-S(O)_tR^7$ (where t is 1 or 2) or $-N(R^7)R^8$;

or R^1 and R^2 together with the carbons to which they are attached form a monocyclic heterocyclic structure selected from the following:



or R^1 and R^2 together with the carbons to which they are attached form the following bicyclic heterocyclic structure:



(where q is 0 to 3, p is 1 to 4 and each R^{15} is hydrogen, alkyl, aralkyl or aryl);

each R^4 is $-R^9$-R^{12}, $-R^9$-R^{13}-R^{11}, $-R^9$-O-R^{10}-R^{11}, $-R^9$-O-R^{12}, $-R^9$-C(O)-R^{10}-R^{11}, $-R^9$-N(R^7)-R^{10}-R^{11}, $-R^9$-$S(O)_t$-R^{10}-R^{11} (where t is 0 to 2), or $-R^9$-$C(F)_2$-R^9-R^{11};

each R^5 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy) or aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy);

each R^6 is independently hydrogen, alkyl, aryl, aralkyl, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^{14}$,

$-C(S)OR^{14}$, $-C(O)N(R^7)R^8$, or $-C(S)N(R^7)R^8$;

each R^7 is independently hydrogen, alkyl, cycloalkyl, aryl, or aralkyl;

R^8 is independently hydrogen, alkyl, aryl, aralkyl, $-C(O)R^7$, $-C(O)OR^{14}$, or cycloalkyl (optionally substituted with one more substituents selected from the group consisting of alkyl, $-N(R^7)_2$, and $-C(O)OR^7$);

each R^9 is independently a direct bond or a straight or branched alkylene chain;

each R^{10} is independently a straight or branched alkylene chain, a straight or branched alkenylene chain, a straight or branched alkynylene chain or a cycloalkylene;

each R^{11} is independently $-C(O)OR^7$, $-C(O)N(R^7)_2$, $-P(O)(OR^7)_2$, $-S(O)_2OR^7$, $-S(O)_2N(H)R^7$ or tetrazole;

R^{12} is aryl (substituted by $-C(O)OR^7$ or $-C(O)N(R^7)_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy) or aralkyl (substituted by $-C(O)OR^7$ or $-C(O)N(R^7)_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy);

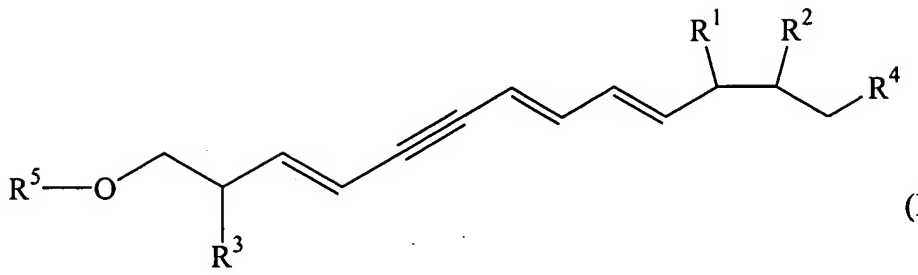
R^{13} is a branched alkylene chain, a straight or branched alkenylene chain or a cycloalkylene; and

R^{14} is alkyl, aryl or aralkyl;

as a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers; or as a cyclodextrin clathrate thereof, or as a pharmaceutically acceptable salt thereof.

9. The pharmaceutical composition of Claim 8 wherein the mammal is a human.

10. A method of treating an inflammatory or autoimmune disorder in a mammal, wherein the method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (II):

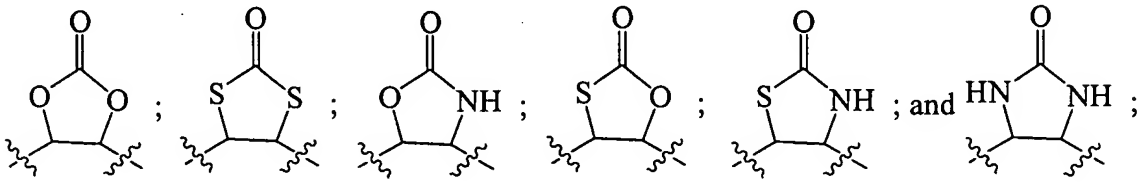


(II)

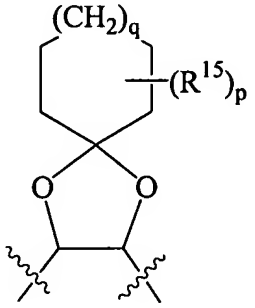
wherein:

each R^1, R^2 and R^3 are independently halo, $-OR^6$, $-SR^6$, $-S(O)_tR^7$ (where t is 1 or 2) or $-N(R^7)R^8$;

or R^1 and R^2 together with the carbons to which they are attached form a monocyclic heterocyclic structure selected from the following:



or R^1 and R^2 together with the carbons to which they are attached form the following bicyclic heterocyclic structure:



(where q is 0 to 3, p is 1 to 4 and each R^{15} is hydrogen, alkyl, aralkyl or aryl);

each R^4 is $-R^9$-R^{12}, $-R^9$-R^{13}-R^{11}, $-R^9$-O-R^{10}-R^{11}, $-R^9$-O-R^{12}, $-R^9$-C(O)-R^{10}-R^{11}, $-R^9$-N(R^7)-R^{10}-R^{11}, $-R^9$-$S(O)_t$-R^{10}-R^{11} (where t is 0 to 2), or $-R^9$-$C(F)_2$-R^9-R^{11};

each R^5 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy) or aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy);

each R^6 is independently hydrogen, alkyl, aryl, aralkyl, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^{14}$,

$-C(S)OR^{14}$, $-C(O)N(R^7)R^8$, or $-C(S)N(R^7)R^8$;

each R^7 is independently hydrogen, alkyl, cycloalkyl, aryl, or aralkyl;

R^8 is independently hydrogen, alkyl, aryl, aralkyl, $-C(O)R^7$, $-C(O)OR^{14}$, or cycloalkyl (optionally substituted with one more substituents selected from the group consisting of alkyl, $-N(R^7)_2$, and $-C(O)OR^7$);

each R^9 is independently a direct bond or a straight or branched alkylene chain;

each R^{10} is independently a straight or branched alkylene chain, a straight or branched alkenylene chain, a straight or branched alkynylene chain or a cycloalkylene;

each R^{11} is independently $-C(O)OR^7$, $-C(O)N(R^7)_2$, $-P(O)(OR^7)_2$, $-S(O)_2OR^7$, $-S(O)_2N(H)R^7$ or tetrazole;

R^{12} is aryl (substituted by $-C(O)OR^7$ or $-C(O)N(R^7)_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy) or aralkyl (substituted by $-C(O)OR^7$ or $-C(O)N(R^7)_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy);

R^{13} is a branched alkylene chain, a straight or branched alkenylene chain or a cycloalkylene; and

R^{14} is alkyl, aryl or aralkyl;

as a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers; or as a cyclodextrin clathrate thereof, or as a pharmaceutically acceptable salt thereof.

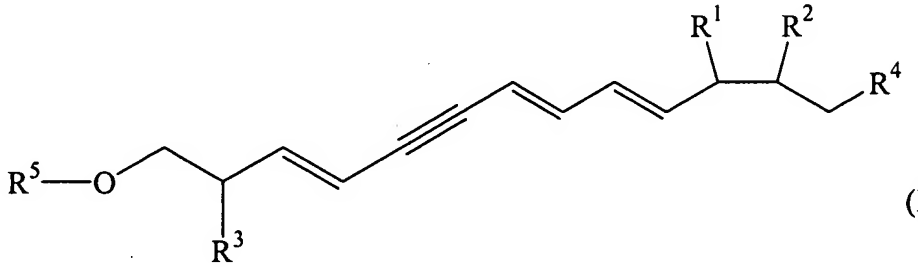
11. The method of Claim 10 wherein the mammal is a human.

12. The method of Claim 11 wherein the inflammatory or autoimmune disorder is selected from the group consisting of the following:

allergic contact dermatitis, allergic rhinitis, chemical and non-specific irritant contact dermatitis, urticaria, atopic dermatitis, psoriasis, acute myocardial ischemia and infarction, acute hemorrhagic or ischemic stroke, multiple sclerosis, rheumatoid arthritis, osteoarthritis and systemic lupus erythematosus, acute and chronic organ transplant rejection, transplant arteriosclerosis and fibrosis, hypertension, atherosclerosis, aneurysm, critical leg ischemia,

peripheral arterial occlusive disease,Reynaud's syndrome, diabetic nephropathy, diabetic neuropathy, and diabetic retinopathy, delayed neurodegeneration in stroke, Alzheimer's disease, Parkinson's disease, benign prostatic hyperplasia, leukemia, lymphoma, prostate cancer, breast cancer, lung cancer, malignant melanoma, renal carcinoma, head and neck tumors and colorectal cancer.

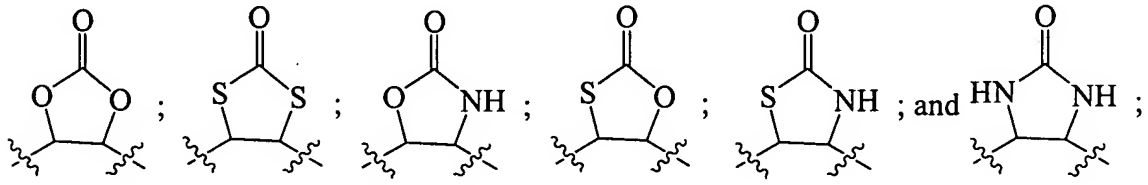
13. A method of treating pulmonary or respiratory tract inflammation in a mammal, wherein the method comprises adminstering to the mammal in need thereof a therapeutically effective amount of a compound of formula (II):



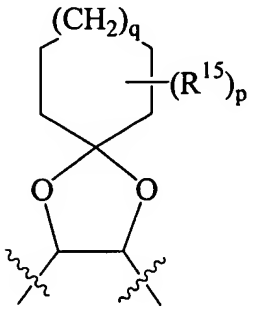
(II)

wherein:

each R^1, R^2 and R^3 are independently halo, $-OR^6$, $-SR^6$, $-S(O)_tR^7$ (where t is 1 or 2) or $-N(R^7)R^8$; or R^1 and R^2 together with the carbons to which they are attached form a monocyclic heterocyclic structure selected from the following:



or R^1 and R^2 together with the carbons to which they are attached form the following bicyclic heterocyclic structure:



(where q is 0 to 3, p is 1 to 4 and each R^{15} is hydrogen, alkyl, aralkyl or aryl);

each R^4 is $-R^9-R^{12}$, $-R^9-R^{13}-R^{11}$, $-R^9-O-R^{10}-R^{11}$, $-R^9-O-R^{12}$, $-R^9-C(O)-R^{10}-R^{11}$, $-R^9-N(R^7)-R^{10}-R^{11}$, $-R^9-S(O)_t-R^{10}-R^{11}$ (where t is 0 to 2), or $-R^9-C(F)_2-R^9-R^{11}$;

each R^5 is aryl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy) or aralkyl (optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy);

each R^6 is independently hydrogen, alkyl, aryl, aralkyl, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^{14}$, $-C(S)OR^{14}$, $-C(O)N(R^7)R^8$, or $-C(S)N(R^7)R^8$;

each R^7 is independently hydrogen, alkyl, cycloalkyl, aryl, or aralkyl;

R^8 is independently hydrogen, alkyl, aryl, aralkyl, $-C(O)R^7$, $-C(O)OR^{14}$, or cycloalkyl (optionally substituted with one more substituents selected from the group consisting of alkyl, $-N(R^7)_2$, and $-C(O)OR^7$);

each R^9 is independently a direct bond or a straight or branched alkylene chain;

each R^{10} is independently a straight or branched alkylene chain, a straight or branched alkenylene chain, a straight or branched alkynylene chain or a cycloalkylene;

each R^{11} is independently $-C(O)OR^7$, $-C(O)N(R^7)_2$, $-P(O)(OR^7)_2$, $-S(O)_2OR^7$, $-S(O)_2N(H)R^7$ or tetrazole;

R^{12} is aryl (substituted by $-C(O)OR^7$ or $-C(O)N(R^7)_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy) or aralkyl (substituted by $-C(O)OR^7$ or $-C(O)N(R^7)_2$ and optionally by one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl and haloalkoxy);

R^{13} is a branched alkylene chain, a straight or branched alkenylene chain or a cycloalkylene; and R^{14} is alkyl, aryl or aralkyl;
as a single stereoisomer, a mixture of stereoisomers, a racemic mixture of stereoisomers; or as a cyclodextrin clathrate thereof, or as a pharmaceutically acceptable salt thereof.

14. The method of Claim 13 wherein the mammal is a human.

15. The method of Claim 10 wherein the inflammatory or autoimmune disorder is selected from the group consisting of the following:

septic or endotoxic shock, hemorrhagic shock, shock-like syndromes, capillary leak syndrome induced by cancer immunotherapy, acute respiratory distress syndrome, traumatic shock, immune- and pathogen-induced pneumonias, immune-complex-mediated pulmonary injury, immune-complex-mediated chronic obstructive pulmonary disease, inflammatory bowel disease, acute renal failure, ischemic bowel disease, immune-complex-mediated glomerulonephritis, insulin-dependent diabetes mellitus, ocular disorders, HIV dementia, encephalitis, inflammatory and neuropathic pain, periodontal disease, and ear infections.

16. The method of Claim 15 wherein the inflammatory or autoimmune disorder is an inflammatory bowel disease selected from the group consisting of Crohn's disease, ulcerative colitis and gastrointestinal ulcers.

17. The method of Claim 16 wherein the inflammatory or autoimmune disorder is Crohn's disease.

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